REMARKS

This Reply is responsive to the Office Action dated March 24, 2003. Entry of the amendments and remarks submitted herein and reconsideration of the claimed subject matter pursuant to 37 CFR §1.112 is respectfully requested.

I. Status of the Claims

Claims 22, 23, 25, 26 and 28-48 were pending in this application at the time of the Office Action dated March 24, 2003. Of the above, claims 30-32, 38 and 40-46 were withdrawn from consideration. No claims have been canceled as a result of this amendment. Accordingly, claims 22, 23, 25, 26, 28, 29, 33-37, 39, 47 and 48 are now pending and under examination.

II. Amendments to the Specification and the Claims

The specification has been amended above to incorporate reference to priority applications, as requested in the Office Action. In addition, the specification has been amended to indicate SEQ ID No. designations where necessary, in accordance with the substitute sequence listing submitted concurrently herewith. The Brief Description of the Drawings was also amended in accordance with the corrected drawings submitted herewith.

Claims 28 and 47 have been amended to incorporate hybridization conditions. Support for these amendments may be found at page 5, lines 9-12, and page 34, lines 17-23. Claim 39 has been amended to indicate a positive process step.

No prohibited new matter has been added by way of any of these amendments.

III. Objections to the Specification

The priority designation has been objected to because the application does not contain reference to the prior applications in the first sentence of the specification or in an application data sheet. Applicants believe that the amendment to the specification above resolves this objection.

The drawings have been objected to as set forth on the PTO-948 form mailed with the Office Action dated March 24, 2003. In response thereto, corrected drawings for Figures 19 and 22-24 have been submitted herewith. The Brief Description of the Drawings has been amended in line with the corrected drawings, accordingly the objection to the drawings and to the corresponding description in the specification may now be withdrawn..

The specification was also objected to for containing sequences that were not identified by SEQ ID Nos. In reviewing the objection, Applicants realized that the sequences in Figure 22 were not included in the sequence listing submitted December 17, 2002. Accordingly, a corrected sequence listing was prepared and is submitted herewith. In addition, the specification has been amended to include SEQ ID No. designations where appropriate, therefore this objection to the specification may now be withdrawn.

IV. Rejections Under 35 U.S.C. §112

Claims 28, 39, 47 and 48 were rejected under 35 U.S.C. §112, second paragraph for alleged indefiniteness. Specifically, claims 28, 47 and 48 were rejected for including

the term "hybridize," which can encompass conditions of varying degrees of stringency. The Office Action suggests that the claims be amended to incorporate specific hybridization conditions. Claims 28 and 47 were amended as suggested to incorporate reference to the hybridization conditions employed in the specification. Accordingly, this rejection may now be withdrawn.

Claim 39 was rejected under §112, second paragraph, for not containing a step that relates back to the preamble. Applicants believe that the amendment to claim 39 above resolves this rejection. In addition, claim 39 was rejected under §112, first and second paragraphs because the specification allegedly has not taught what transduction signal is appropriate. Applicants respectfully traverse this second ground for the rejection.

It is clear from the specification at page 24, line 23 to page 26, line 15, and further at page 30, lines 6-19, how agonist and antagonist activity may be detected. Indeed, the specification describes how SM-11044 was shown to relax KCl-induced tonus in a rat colon smooth muscle segment under blockade of α-, β1- and β2-ARs in the presence of 10 μM phentolamine and 1 μM propanolol (page 24, lines 24-27), and how cyanopindolol antagonized SM-11044-induced rat colon relaxation in a concentration-dependent manner (page 25, lines 23-25).

Further, as disclosed at page 30, lines 6-8, agonist effects include relaxant responses in guinea pig ileum and rat colon intestines, and inhibition of guinea pig eosinophil chemotaxis. Therefore, the step of measuring an appropriate transduction signal can be carried out using either one of these effects. Methods of measuring eosinophil chemotaxis were well known by the priority date of the application, as shown

in the attached article, Sugasawa and Morooka, 1992, *Recent Advances in Cellular and Molecular Biology*, 3: 223-227. This article reports the results of an evaluation conducted by the same method as that used in the present application. See, *e.g.*, p. 225, lines 12-23.

Given that the specification clearly discloses transduction signals for measuring the agonist and antagonist activities, and that assays for measuring such activities were well known in the art at the time the present invention was filed, reconsideration and withdrawal of the rejections of claim 39 under §112, first and second paragraphs, is respectfully requested.

Claims 22, 25, 29, 33, 34, 36, 37, 47 and 48 were rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabled for polynucleotides encoding a protein of SEQ ID No. 14 and the portion thereof capable of binding ICYP, allegedly fails to enable other polynucleotides. Essentially, the Office Action alleges that the specification fails to provide sufficient guidance for polypeptides that are not 100% identical to SEQ ID No. 14, *i.e.*, substitutions, deletions and insertions, but which still retain a desired property of the polypeptide of SEQ ID No. 14. Applicants respectfully traverse the rejection.

The claimed genus of proteins encompasses natural species variants. The skilled artisan could readily isolate ICYP-binding proteins from other species that meet the claimed limitations, given that the specification demonstrates the existence of the protein in rats, and that the CnBr fragment of the rat protein used to identify and clone the human protein (SEQ ID No. 6) demonstrates almost 100% homology to the corresponding human sequence (see Example 3 starting on page 32). This suggests that this family of

proteins is highly conserved across species, and that the same, well known methodology used to clone the human gene could also be used without undue experimentation to clone the gene from other species.

Furthermore, the claimed protein is defined in functional terms according to which one skilled in the art could readily identify proteins falling within the scope of the claims. The skilled artisan need not be instructed as to which substitutions, deletions or insertions are included in the invention, since the claimed genus is defined according to functions that may be readily tested according to the tests disclosed in the specification as well as those described above.

Applicants also disagree with several bases for the rejection. For instance, the Office Action asserts at page 8 that the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation, *i.e.*, to identify active variants. The standard for enablement permits a certain amount of experimentation so long as such experimentation is not undue.

The Office Action further asserts at page 9 that a large quantity of experimentation would be necessary "to generate the infinite number of variants recited in the claims and possibly screen the same for activity." However, the skilled artisan need not identify all variants encompassed by the claims to benefit from the invention. Rather, the skilled artisan merely needs to be taught how to determine whether any given variant falls within the scope of the claims, and clearly, the skilled artisan may readily do so given the function and sequence fragments recited in the claims.

The Office Action also notes at page 8 that no disorder or phenotype has been asserted to correlate with a variant, and that Applicant has not provided guidance as to

what properties of sequence variants might be desired. This is clearly untrue since a variant falling within the scope of the invention must have the functional characteristics and physical properties recited in the claims.

With regard to natural variants, as mentioned above, the CnBr fragment of the rat protein used to identify and clone the human protein (SEQ ID No. 6) demonstrates almost 100% homology to the corresponding human sequence (SEQ ID No. 5) (see Example 3 starting on page 32). This suggests that this family of proteins is highly conserved across species, and that the same, well known methodology used to clone the human gene could also be used without undue experimentation to clone natural variants from other species. Submitted herewith is a §1.132 declaration by Toshinari Sugasawa, one of the inventors of the subject application, describing the results of BLAST database searches using the fragments represented by SEQ ID Nos. 5 and 6.

As shown in the attached declaration, when conducted with the amino acid sequence of SEQ ID No. 5, the BLAST search revealed 14 clones showing 100% homology in the region of the fragment represented by SEQ ID No. 5. Most all of these clones reveal homologous animal ICYP receptors, including the receptor from human, mouse, *C. elegans*, zebra fish, etc. (Note that TM9SF3 (transmembrane position 9 superfamily member 3) and SMBP (SM-11044 binding protein) and ICYP receptor are the same protein.) When the search was conducted with the amino acid sequence of SEQ ID No. 6, which comprises an "X" in the amino acid sequence and would identify clones with fragments having at least 87% identity, 16 clones were identified including chicken and fruit fly TM9SF3. Thus, the fragment used in Example 3 of the specification to

identify human ICYP receptor cDNA using the BLAST program could also be used in the same manner to identify natural variants from other species.

In view of the remarks presented above and the attached declaration by Dr. Sugasawa, reconsideration and withdrawal of the enablement rejection under 35 U.S.C. §112, first paragraph, are respectfully requested.

Claims 22, 25, 29, 33, 34, 36, 37, 47 and 48 were also rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification so as to reasonably convey that the inventors, at the time the application was filed, had possession of the claimed invention. Essentially, the claims are rejected because they encompass sequences that were not described in the specification. The Office Action also refers to *Regents of the University of California v. Eli Lilly & Co.* as standing for the premise that one must disclose a representative number of cDNAs defined by nucleotide sequence in order to obtain a genus claim. Applicants respectfully traverse the rejection.

With regard to the reliance on *Regents of the University of California v. Eli Lilly & Co.*, the merits of each case must be examined on a case-by-case basis, and *Lilly* does not suggest otherwise. Moreover, *Lilly* is only relevant to the particular circumstances surrounding that case, which happened to occur at a time when the art of biotechnology was much less developed than it is now. In any case, in contrast to what is stated in the Office Action, *Lilly* does not stand for the sweeping premise that a genus polynucleotide claim can only be supported by the disclosure of a representative number of nucleic acid sequences.

According to the Written Description Guidelines (FR, Vol. 66, No. 4, page 1099, January 5, 2001) (see copy attached hereto), "[a]ctual reduction to practice may be crucial in the relatively rare instances where the level of knowledge and level of skill are such that those of skill in the art cannot describe a composition structurally, or specify a process of making a composition by naming components and combining steps" (with emphasis, page 1101). In fact, the Guidelines state at page 1106 that:

> An applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. (With emphasis.)

Footnote 42 of the Guidelines further defines some identifying characteristics for biomolecules to include sequence, structure, binding affinity, binding specificity, molecular weight, length, unique cleavage by particular enzymes, detailed restriction maps, a comparison of enzymatic activities, or antibody cross-reactivity (see page 1110 of the FR Notice). There is no basis in the Guidelines or in the case law that supports the rejection. *See, e.g.*, the Guidelines, p. 1101, col. 3, first paragraph ("There is no basis for a *per se* rule requiring disclosure of complete DNA sequences or limiting claims to only the sequence disclosed).

Thus, given the state of the art at the time of the invention pertaining to the identification and cloning of nucleic acids and the level of physical and functional characterization of the novel protein in the specification, we believe that the skilled artisan would immediately see upon reading the specification that Applicant was in possession of the claimed genus of polypeptides and the genus of nucleic acids that encode the polypeptide genus at the time the application was filed. Reconsideration and withdrawal of the written description rejection under §112, first paragraph, are respectfully requested.

Claim 35 was rejected under §112, first paragraph, because it is unclear whether the plasmid recited in the claim is publicly available. Applicants respectfully note that the specification describes at page 52, lines 20-24 (in original claim 14) that the plasmid was deposited with the Collection Nationale de Cultures de Microorganismes (CNCM) on December 10, 1996, under the accession number I-1795. Further, Applicants respectfully submit that this deposit was made under the terms of the Budapest treaty. A statement by Applicants' representative confirming that the deposit was made in accordance with the Budapest is attached hereto. Reconsideration and withdrawal of the rejection of claim 35 under §112, first paragraph, are respectfully requested.

This reply is fully responsive to the Office Action dated March 24, 2003. Therefore, a Notice of Allowance is next in order and is respectfully requested.

Except for issue fees payable under 37 CFR §1.18, the commissioner is hereby authorized by this paper to charge any additional fees during the pendency of this application including fees due under 37 CFR §1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 CFR §1.136(a)(3).

If the Examiner has any further questions relating to this Reply or to the application in general, he is respectfully requested to contact the undersigned by telephone so that allowance of the present application may be expedited.

Respectfully submitted,

Morgan, Lewis & Bockius LLP

for Elizabeth C Weiman
Bonnie Weiss McLeod Reg. No.
Registration No. 43,255 44,478

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Morgan, Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Ave., N.W.
Washington, D.C. 20004
202-739-3000
202-739-3001